

### REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, attached as Appendix A is a Version With Markings to Show Changes Made.

The rejection of claims 3-47 under 35 U.S.C. § 112, second paragraph, for indefiniteness is respectfully traversed in view of the above amendments and the following remarks.

Applicants have amended claims 3, 7, 10, 11, 17, 22, 23, 29-31, 33-36, and 41 to recite that the reaction is carried out "for a time and under conditions effective" (additions underlined) to produce a product. Since the additional language was encompassed by the broader phrase "under conditions effective," this amendment does not relate to patentability.

With regard to the rejection of claims 34 and 35, applicants note that claim 33 is not limited to a process in which the carrier, hydrazide, and antibody are combined together in one reaction. Accordingly, claims 34 and 35, which further define claim 33 to specify a sequence of reaction steps, are proper dependent claims. However, in the interests of expeditious prosecution, applicants have amended claims 34 and 35 to make them independent claims.

With regard to the rejection of claims 36 and 41, applicants have amended claims 36, 38, 39, 41, 45, and 46 to further define the word "spacer." It is the position of the U.S. Patent and Trademark Office ("PTO") that it appears that the "spacer" of claim 36 is different than the "spacer" of claim 41. In particular, it is the PTO's position that the implication is that the reactive groups of the "spacer" in claim 41 are present in order to achieve coupling between the antibody and the "A" group, whereas in claim 36, the implication is that in the final product (i.e., HO-antibody-spacer-(A)<sub>n</sub>), reactive groups are present. Thus, the PTO argues that the term "spacer" should be defined differently in claims 36 and 41. Applicants respectfully disagree.

As described in the specification of the present application at page 25, line 12 to page 27, line 21, and as set forth in claim 41, the "spacer" includes groups capable of bonding with the "-NHNH-" group of the A moiety and the antibody, i.e., "a first reactive terminus and one or more second reactive termini . . . with one or more of the one or more second reactive termini" (emphasis added) (see claim 41) being reacted with a hydrazide. Therefore, one or more of the second reactive termini (i.e., reactive groups) of the spacer are present in order to achieve coupling with the "A" group, however, not all of the one or more second reactive termini must be used in order to achieve coupling with the "A" group when

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more than one second reactive termini is present. Thus, one or more reactive groups may be present in the final product (i.e., HO-antibody-spacer-(A)<sub>n</sub>). Accordingly, in both claim 36 and claim 41, the final product (i.e., HO-antibody-spacer-(A)<sub>n</sub>) may or may not include reactive groups.

In view of the all of the foregoing, applicants submit that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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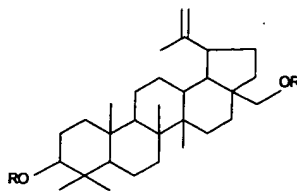
# Appendix A

## Version With Markings to Show Changes Made

In reference to the amendments made herein to claims 3, 7, 10, 11, 17, 22-23, 29-31, 33-36, 38-39, 41, and 45-46, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

### In the Claims:

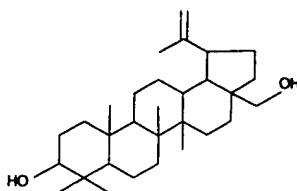
3. (Twice-Amended) A method of synthesizing a diether having the formula:



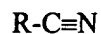
wherein R is alkyl,

said method comprising:

alkylating a dialcohol having the formula:



with a nitrile having the formula:



for a time and under conditions effective to form the diether, and  
isolating the diether.

7. (Twice-Amended) A method of preparing betulonic aldehyde comprising:

oxidizing betulinol with chromium anhydride in acetone in the presence of sulfuric acid for a time and under conditions effective to produce betulonic aldehyde, and

isolating the betulonic aldehyde.

10. (Twice-Amended) A method [according to claim 7, wherein said oxidizing further comprises] of preparing betulonic aldehyde comprising:

reacting betulinol with chromium anhydride in acetone in the presence of sulfuric acid for a time and under conditions effective to produce a reaction mixture that includes betulonic aldehyde;

cooling the reaction mixture; [and]

adding water to the reaction mixture, whereby a sediment containing betulonic aldehyde forms; and

isolating the betulonic aldehyde.

11. (Amended) A method [according to claim 10 further] of preparing betulonic aldehyde comprising:

reacting betulinol with chromium anhydride in acetone in the presence of sulfuric acid for a time and under conditions effective to produce a reaction mixture that includes betulonic aldehyde;

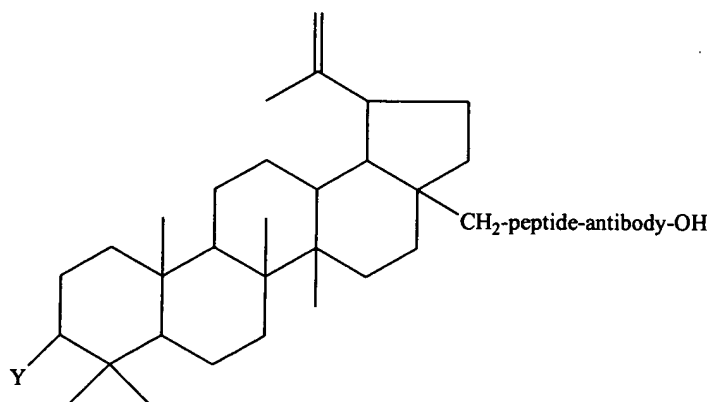
cooling the reaction mixture;

adding water to the reaction mixture, whereby a sediment containing betulonic aldehyde forms;

[recrystallizing] crystallizing the sediment; and

isolating the betulonic aldehyde.

17. (Twice-Amended) A method of producing a betulinol-antibody conjugate having the formula:

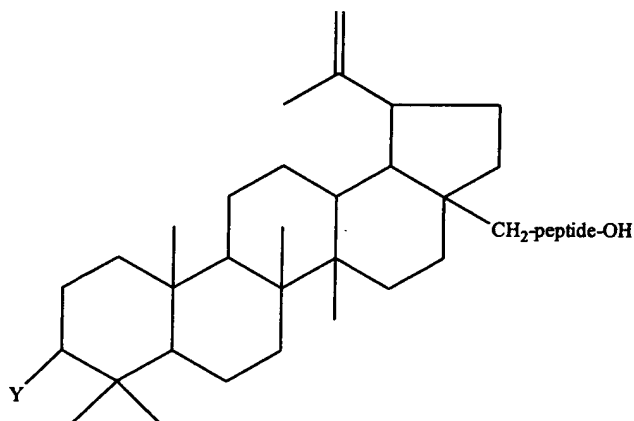


wherein

Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group,

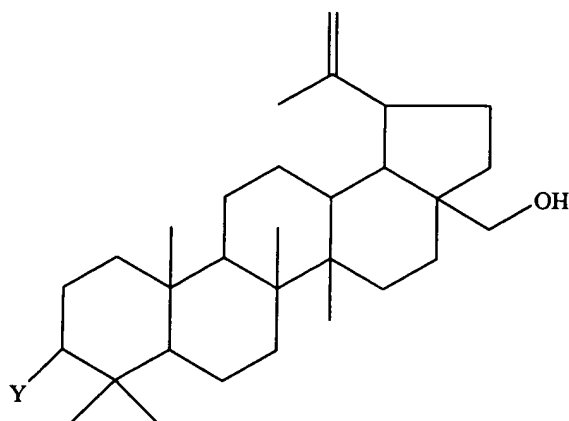
said method comprising:

reacting a betulinol peptide having the formula:



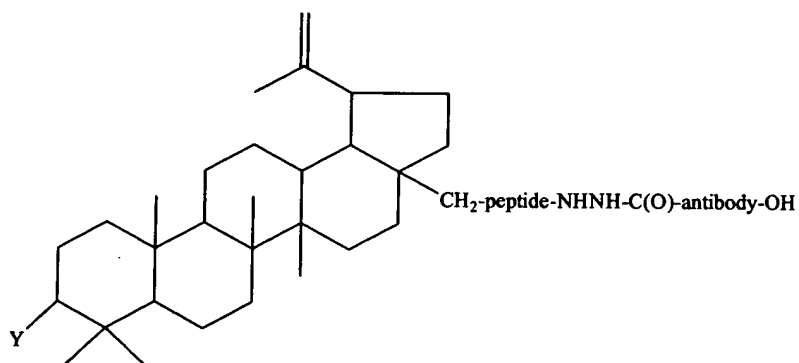
with an antibody having the formula H-antibody-OH for a time and under conditions effective to produce the betulinol-antibody conjugate, and  
isolating the betulinol-antibody conjugate.

22. (Twice-Amended) A method according to claim 17, wherein said betulinol peptide is obtained by a process comprising:  
reacting a compound having the formula:



with a peptide having the formula H-peptide-OH for a time and under conditions effective to produce the betulinol peptide, and  
isolating the betulinol peptide.

23. (Twice-Amended) A method of producing a betulinol-antibody conjugate having the formula:

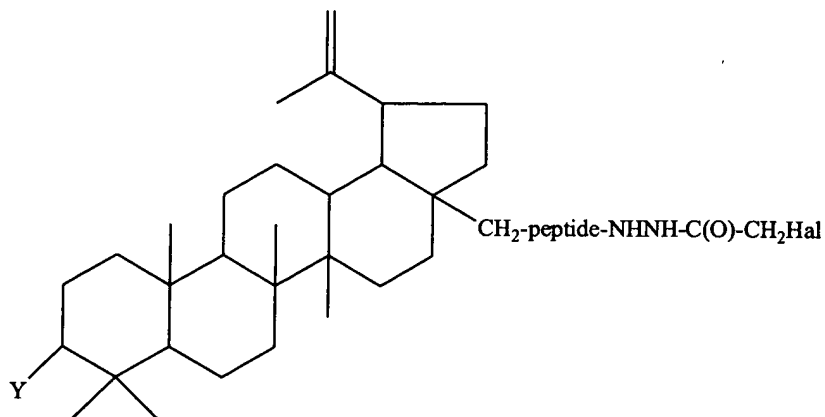


wherein

Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group,

said method comprising:

reacting a haloacetylhydrazide having the formula:



wherein

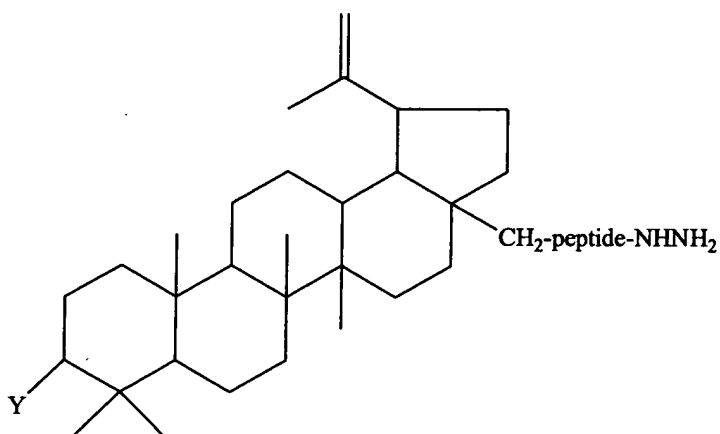
Hal is a halogen

with an antibody having the formula  $\text{H-antibody-OH}$  for a time and under conditions effective to produce the betulinol-antibody conjugate, and

isolating the betulinol-antibody conjugate.

29. (Twice-Amended) A method according to claim 23, wherein said haloacetylhydrazide is obtained by a process comprising:

reacting a hydrazide having the formula:

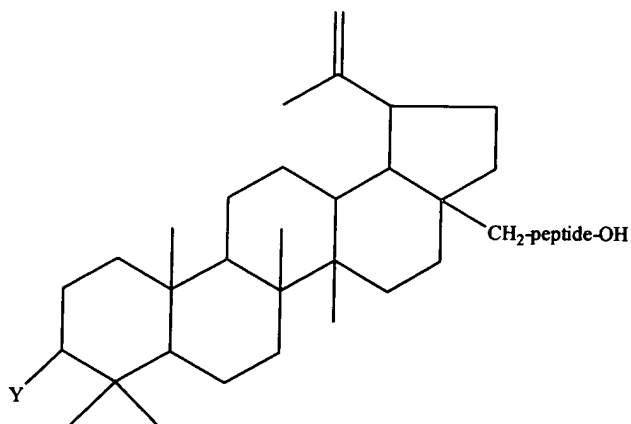


with a *para*-nitrophenyl  $\alpha$ -haloacetate for a time and under conditions effective to produce the haloacetylhydrazide, and

isolating the haloacetylhydrazide.

30. (Twice-Amended) A method according to claim 29, wherein said hydrazide is obtained by a process comprising:

reacting a betulinol peptide having the formula:

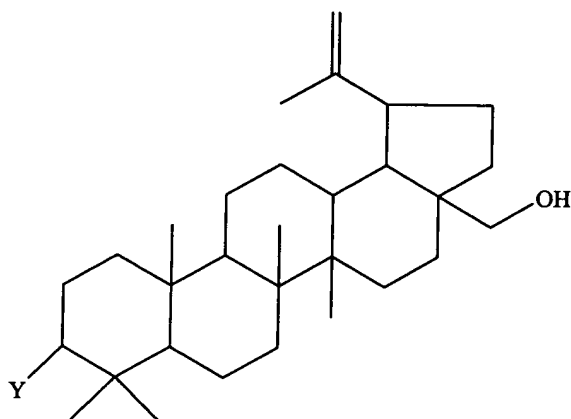


with hydrazine hydrate for a time and under conditions effective to produce the hydrazide, and

isolating the hydrazide.

31. (Twice-Amended) A method according to claim 30, wherein said betulinol peptide is obtained by a process comprising:

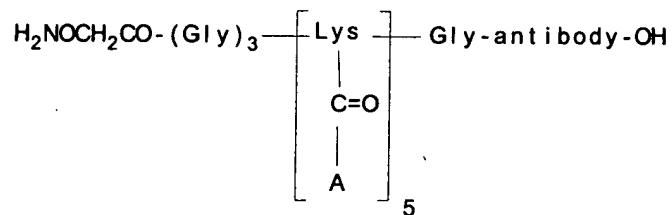
reacting a compound having the formula:



with a peptide having the formula H-peptide-OH for a time and under conditions effective to produce the betulinol peptide, and

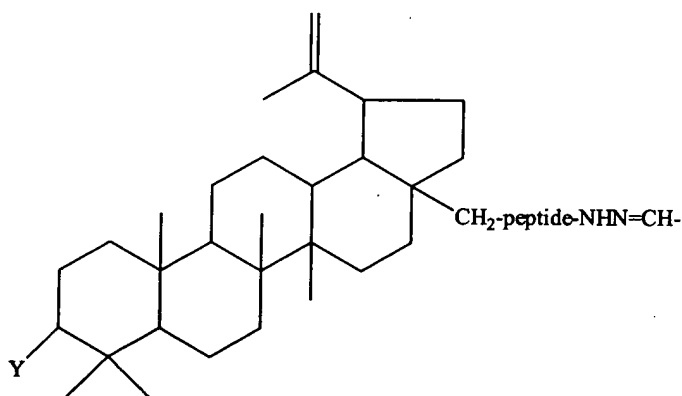
isolating the betulinol peptide.

33. (Twice-Amended) A method of producing a betulinol-antibody conjugate having the formula:



wherein

each "A" moiety is independently selected from the group consisting of a -CHO group and a moiety having the formula:

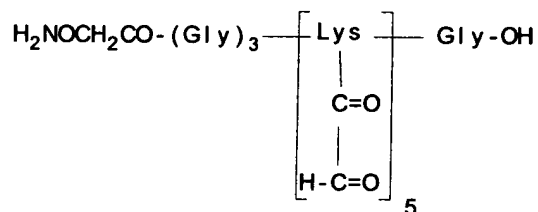


provided that at least one of A is not -CHO; and

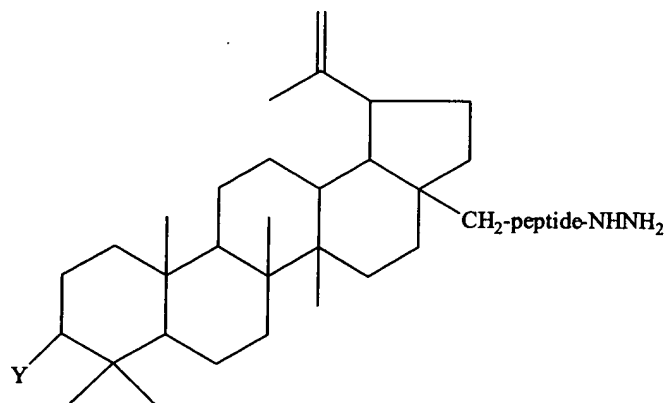
Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group,

said method comprising:

reacting a carrier molecule having the formula:



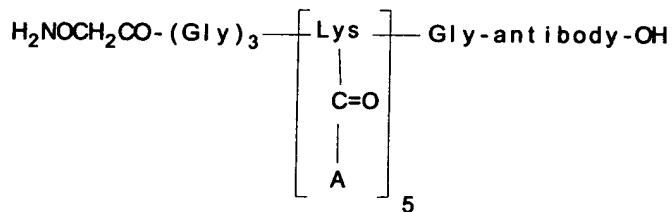
[with] a hydrazide having the formula:



and an antibody having the formula H-antibody-OH for a time and under conditions effective to produce the betulinol-antibody conjugate, and

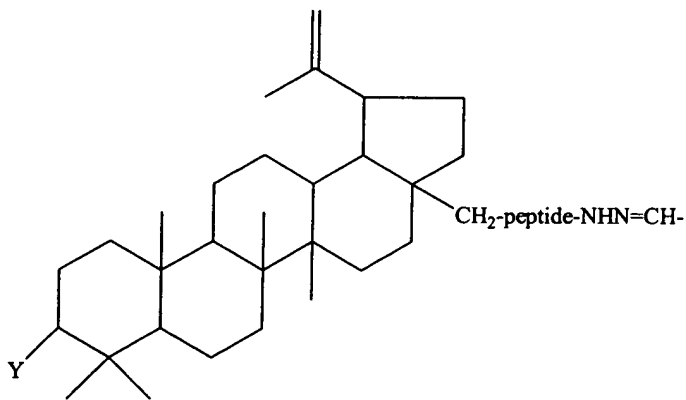
isolating the betulinol-antibody conjugate.

34. (Twice-Amended) A method [according to claim 33, wherein said reacting the carrier molecule comprises] of producing a betulinol-antibody conjugate having the formula:



wherein

each "A" moiety is independently selected from the group consisting of a -CHO group and a moiety having the formula:

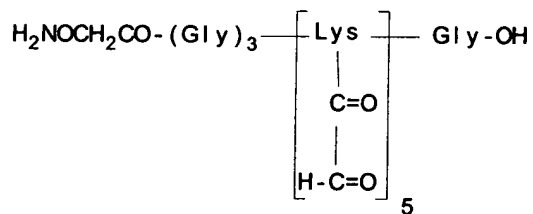


provided that at least one of A is not -CHO; and

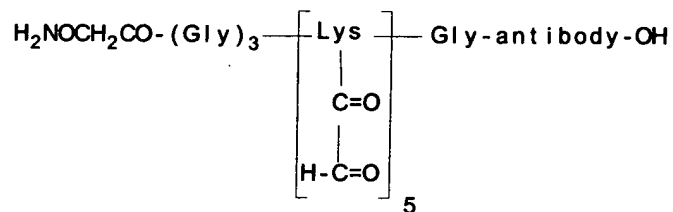
Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group,

said method comprising:

reacting [the] a carrier molecule having the formula:

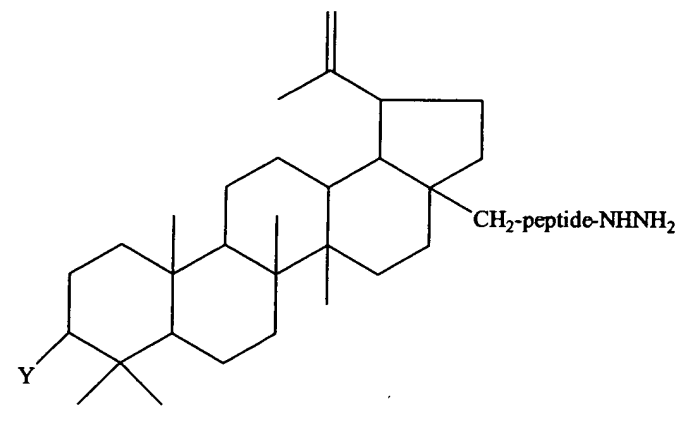


with [the] an antibody having the formula H-antibody-OH for a time and under conditions effective to produce an antibody-bound carrier molecule having the formula:



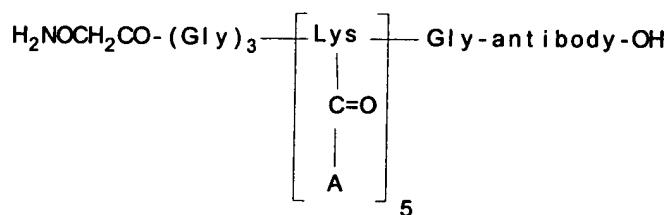
and

reacting the antibody-bound carrier molecule with a [the] hydrazide having the formula:



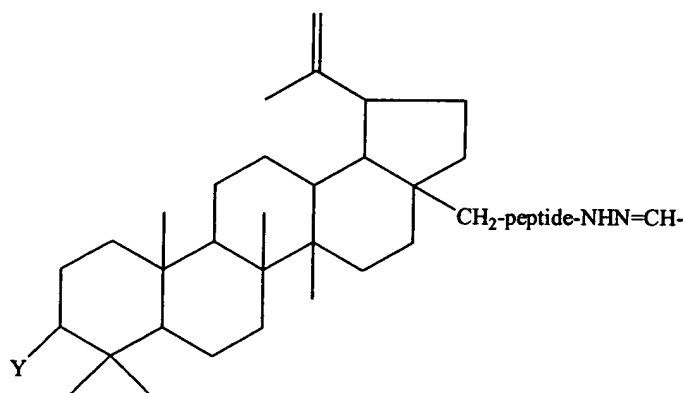
for a time and under conditions effective to produce the betulinol-antibody conjugate, and  
isolating the betulinol-antibody conjugate.

35. (Twice-Amended) A method [according to claim 33, wherein said reacting the carrier molecule comprises] of producing a betulinol-antibody conjugate having the formula:



wherein

each "A" moiety is independently selected from the group consisting of a -CHO group and a moiety having the formula:

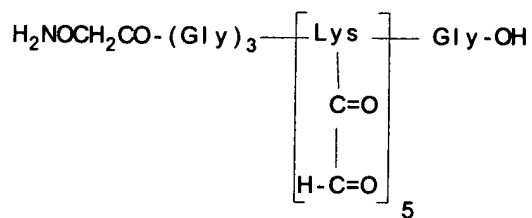


provided that at least one of A is not -CHO; and

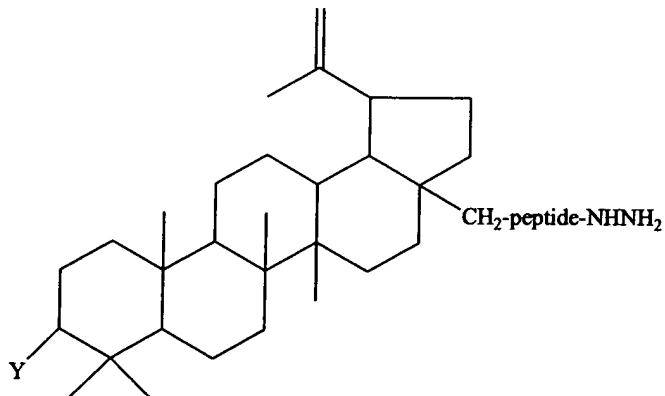
Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group,

said method comprising:

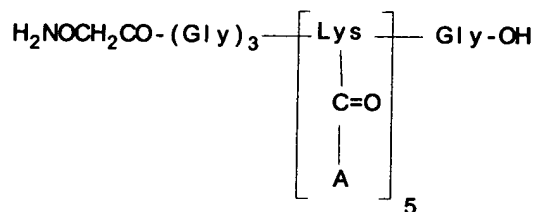
reacting [the] a carrier molecule having the formula:



with [the] a hydrazide having the formula:

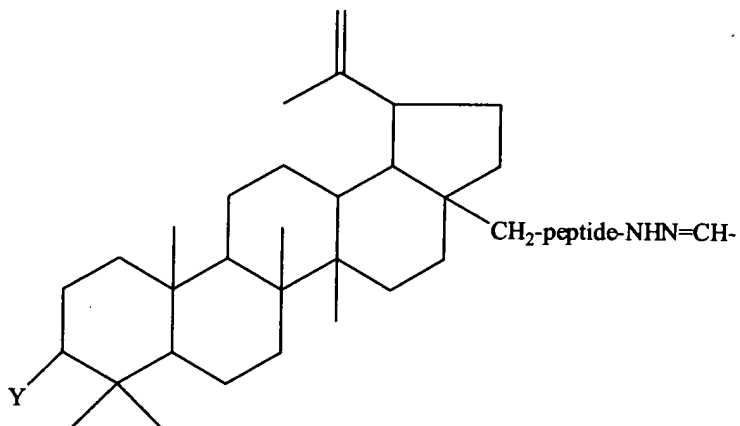


for a time and under conditions effective to produce a betulinol-bound carrier molecule having the formula:



wherein

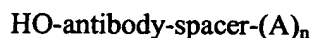
at least one A is a moiety having the formula:



and

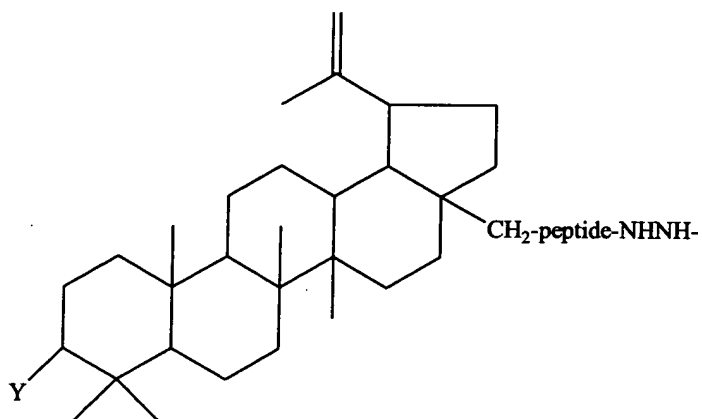
reacting the betulinol-bound carrier molecule with [the] an antibody having the formula H-antibody-OH for a time and under conditions effective to produce the betulinol-antibody conjugate, and  
isolating the betulinol-antibody conjugate.

36. (Twice-Amended) A betulinol-antibody conjugate having the formula:



wherein

A is a moiety having the formula:



Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group; [and]

“spacer” is multivalent moiety bonded to the antibody and (A)<sub>n</sub>;  
and

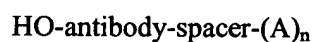
n is an integer from 1 to 100.

38. (Twice-Amended) A betulinol-antibody conjugate according to claim 36, wherein “spacer” is a multivalent moiety produced from a diamine derivative of

polyethylene glycol having 2-(pyridyldithio)-propionyl and N-hydroxysuccinimide ester groups bonded thereto.

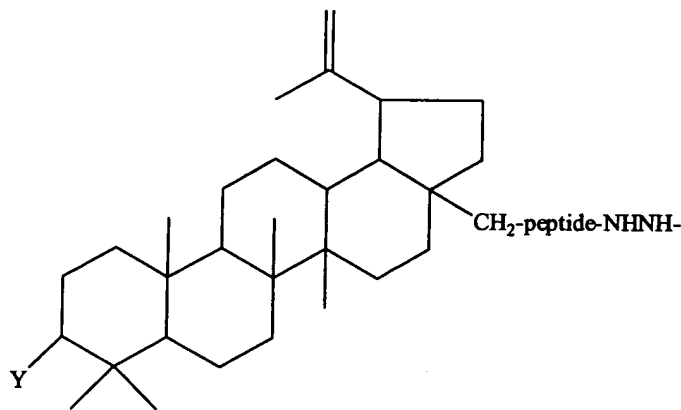
39. (Twice-Amended) A betulinol-antibody conjugate according to claim 36, wherein "spacer" is a multivalent moiety produced from a branched form of polyethylene glycol propionic acid N-hydroxysuccinimide ester.

41. (Twice-Amended) A method of producing a betulinol-antibody conjugate having the formula:



wherein

A is a moiety having the formula:



Y is a hydroxy group, an alkoxy group, or an alkanoyloxy group; [and]

"spacer" is multivalent moiety bonded to the antibody and (A)<sub>n</sub>;  
and

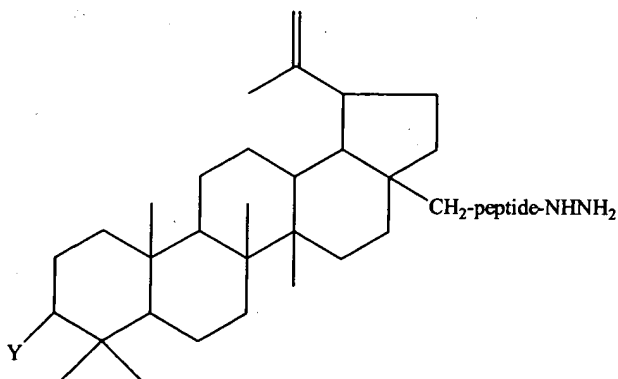
n is an integer from 1 to 100,

said method comprising:

providing a "spacer" having a first reactive terminus and one or more second reactive termini;

reacting an antibody with the first reactive terminus;

reacting a hydrazide having the formula:



with one or more of the one or more second reactive termini for a time and under conditions effective to produce the betulinol-antibody conjugate; and  
isolating the betulinol-antibody conjugate.

45. (Twice-Amended) A method according to claim 41, wherein  
“spacer” is a multivalent moiety produced from a diamine derivative of polyethylene glycol having 2-(pyridyldithio)-propionyl and N-hydroxysuccinimide ester groups bonded thereto.

46. (Twice-Amended) A method according to claim 41, wherein  
“spacer” is a multivalent moiety produced from a branched form of polyethylene glycol propionic acid N-hydroxysuccinimide ester.